UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION **This document relates to**: *Track Three Cases*	**MDL No. 2804** **Case No. 17-md-2804** **Judge Dan Aaron Polster**

DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

EXHIBIT 10

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The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy

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I focus on issues surrounding the promotion and marketing of controlled drugs and their regulatory oversight. Compared with noncontrolled drugs, controlled drugs, with their potential for abuse and diversion, pose different public health risks when they are overpromoted and highly prescribed. An in-depth analysis of the promotion and marketing of OxyContin illustrates some of the associated issues.

Modifications of the promotion and marketing of controlled drugs by the pharmaceutical industry and an enhanced capacity of the Food and Drug Administration to regulate and monitor such promotion can have a positive impact on the public health. (*Am J Public Health.* 2009;99:221–227. doi: 10.2105/AJPH.2007.131714)

CONTROLLED DRUGS, WITH their potential for abuse and diversion, can pose public health risks that are different from—and more problematic than—those of uncontrolled drugs when they are overpromoted and highly prescribed. An in-depth analysis of the promotion and marketing of OxyContin (Purdue Pharma, Stamford, CT), a sustained-release oxycodone preparation, illustrates some of the key issues. When Purdue Pharma introduced OxyContin in 1996, it was aggressively marketed and highly promoted. Sales grew from $48 million in 1996 to almost $1.1 billion in 2000.[1] The high availability of OxyContin correlated with increased abuse, diversion, and addiction, and by 2004 OxyContin had become a leading drug of abuse in the United States.[2]

Under current regulations, the Food and Drug Administration (FDA) is limited in its oversight of the marketing and promotion of controlled drugs. However, fundamental changes in the promotion and marketing of controlled drugs by the pharmaceutical industry, and an enhanced capacity of the FDA to regulate and monitor such promotion, can positively affect public health.

OxyContin's commercial success did not depend on the merits of the drug compared with other available opioid preparations. The *Medical Letter on Drugs and Therapeutics* concluded in 2001 that oxycodone offered no advantage over appropriate doses of other potent opioids.[3] Randomized double-blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given 4 times daily showed comparable efficacy and safety for use with chronic back pain[4] and cancer-related pain.[5,6] Randomized double-blind studies that compared OxyContin with controlled-release morphine for cancer-related pain also found comparable efficacy and safety.[7–9] The FDA's medical review officer, in evaluating the efficacy of OxyContin in Purdue's 1995 new drug application, concluded that OxyContin had not been shown to have a significant advantage over conventional, immediate-release oxycodone taken 4 times daily other than a reduction in frequency of dosing.[10] In a review of the medical literature, Chou et al. made similar conclusions.[11]

The promotion and marketing of OxyContin occurred during a recent trend in the liberalization of the use of opioids in the treatment of pain, particularly for chronic non–cancer-related pain. Purdue pursued an "aggressive" campaign to promote the use of opioids in general and OxyContin in particular.[1,12–17] In 2001 alone, the company spent $200 million[18] in an array of approaches to market and promote OxyContin.

PROMOTION OF OXYCONTIN

From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona, and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses-paid symposia, where they were recruited and trained for Purdue's national speaker bureau.[19(p22)] It is well documented that this type of pharmaceutical company symposium influences physicians' prescribing,

even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns.[20]

One of the cornerstones of Purdue's marketing plan was the use of sophisticated marketing data to influence physicians' prescribing. Drug companies compile prescriber profiles on individual physicians—detailing the prescribing patterns of physicians nationwide—in an effort to influence doctors' prescribing habits. Through these profiles, a drug company can identify the highest and lowest prescribers of particular drugs in a single zip code, county, state, or the entire country.[21] One of the critical foundations of Purdue's marketing plan for OxyContin was to target the physicians who were the highest prescribers for opioids across the country.[1,12–17,22] The resulting database would help identify physicians with large numbers of chronic-pain patients. Unfortunately, this same database would also identify which physicians were simply the most frequent prescribers of opioids and, in some cases, the least discriminate prescribers.

A lucrative bonus system encouraged sales representatives to increase sales of OxyContin in their territories, resulting in a large number of visits to physicians with high rates of opioid prescriptions, as well as a multifaceted information campaign aimed at them. In 2001, in addition to the average sales representative's annual salary of $55 000, annual bonuses averaged $71 500, with a range of $15 000 to nearly $240 000. Purdue paid $40 million in sales incentive bonuses to its sales representatives that year.[19]

From 1996 to 2000, Purdue increased its internal sales force from 318 sales representatives to 671, and its total physician call list from approximately 33 400 to 44 500 to approximately 70 500 to 94 000 physicians.[19] Through the sales representatives, Purdue used a patient starter coupon program for OxyContin that provided patients with a free limited-time prescription for a 7- to 30-day supply. By 2001, when the program was ended, approximately 34 000 coupons had been redeemed nationally.[19]

The distribution to health care professionals of branded promotional items such as OxyContin fishing hats, stuffed plush toys, and music compact discs ("Get in the Swing With OxyContin") was unprecedented for a schedule II opioid, according to the Drug Enforcement Administration.[19]

Purdue promoted among primary care physicians a more liberal use of opioids, particularly sustained-release opioids. Primary care physicians began to use more of the increasingly popular OxyContin; by 2003, nearly half of all physicians prescribing OxyContin were primary care physicians.[19] Some experts were concerned that primary care physicians were not sufficiently trained in pain management or addiction issues.[23] Primary care physicians, particularly in a managed care environment of time constraints, also had the least amount of time for evaluation and follow-up of patients with complicated chronic pain.

Purdue "aggressively" promoted the use of opioids for use in

TABLE 1—Distribution of OxyContin, Oxycodone (Excluding OxyContin), and Hydrocodone per 100 000 Population: Virginia, West Virginia, and Kentucky, 2000

	Distribution in Grams per 100 000 Population		
State and County	OxyContin	Oxycodone (Excluding OxyContin)	Hydrocodone
Virginia			
Dickenson	25 801	2 777	16 692
Lee	23 398	6 232	8 445
Buchanan	19 138	3 235	15 996
Scott	18 328	4 946	12 274
Roanoke City	17 856	2 808	7 201
Tazewell	17 135	3 482	27 714
Winchester City	15 242	6 764	14 057
Manassas City	14 735	5 920	5 511
Fauquier	14 396	6 935	4 434
Wythe	14 236	3 165	8 812
Kentucky			
Cumberland	22 113	1 486	8 148
Perry	20 996	6 145	27 413
Harlan	19 359	3 121	10 141
Leslie	18 221	4 017	16 925
Whitley	13 438	3 410	19 532
Greenup	13 222	5 151	44 872
McCreary	12 573	3 026	12 996
Clinton	12 517	2 911	14 892
Bell	11 739	3 118	26 037
Clay	11 563	3 260	21 093
West Virginia			
Pocahontas	17 318	3 605	17 651
Raleigh	16 813	5 959	8 718
Berkeley	16 299	5 254	5 009
Logan	16 153	2 224	22 950
McDowell	15 770	3 200	24 235
Greenbrier	15 752	2 539	12 380
Mercer	15 040	3 306	21 175
Hancock	13 465	4 327	8 831
Harrison	12 409	3 407	12 658
Cabell	11 665	3 608	13 018
US average	3 750	1 761	5 083

Source. Office of Diversion Control, Drug Enforcement Administration.[67]
Note. Data are for the counties or independent cities with the highest quantities of opioids (in grams) prescribed in each of the 3 states.

the "non-malignant pain market."[15(p187)] A much larger market than that for cancer-related pain, the non–cancer-related pain market constituted 86% of the total opioid market in 1999.[17] Purdue's promotion of OxyContin for the treatment of non–cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670 000 in 1997 to about 6.2 million in 2002, whereas prescriptions for cancer-related pain increased about fourfold during that same period.[19] Although the science and consensus for the use of opioids in the treatment of acute pain or pain associated with cancer are robust, there is still much controversy in medicine about the use of opioids for chronic non–cancer-related pain, where their risks and benefits are much less clear. Prospective, randomized, controlled trials lasting at least 4 weeks that evaluated the use of opioids for chronic, non–cancer-related pain showed statistically significant but small to modest improvement in pain relief, with no consistent improvement in physical functioning.[24–38] A recent review of the use of opioids in chronic back pain concluded that opioids may be efficacious for short-term pain relief, but longer-term efficacy (>16 weeks) is unclear.[39]

In the long-term use of opioids for chronic non–cancer-related pain, the proven analgesic efficacy must be weighed against the following potential problems and risks: well-known opioid side effects, including respiratory depression, sedation, constipation, and nausea; inconsistent improvement in functioning; opioid-induced hyperalgesia; adverse hormonal and immune effects of long-term opioid treatment; a high incidence of prescription opioid abuse behaviors; and an ill-defined and unclarified risk of iatrogenic addiction.[40]

MISREPRESENTING THE RISK OF ADDICTION

A consistent feature in the promotion and marketing of OxyContin was a systematic effort to minimize the risk of addiction in the use of opioids for the treatment of chronic non–cancer-related pain. One of the most critical issues regarding the use of opioids in the treatment of chronic non–cancer-related pain is the potential of iatrogenic addiction. The lifetime prevalence of addictive disorders has been estimated at 3% to 16% of the general population.[41] However, we lack any large, methodically rigorous prospective study addressing the issue of iatrogenic addiction during long-term opioid use for chronic nonmalignant pain.[42]

In much of its promotional campaign—in literature and audiotapes for physicians, brochures and videotapes for patients, and its "Partners Against Pain" Web site—Purdue claimed that the risk of addiction from OxyContin was extremely small.[43–49]

Purdue trained its sales representatives to carry the message that the risk of addiction was "less than one percent."[50(p99)] The company cited studies by Porter and Jick,[51] who found iatrogenic addiction in only 4 of 11 882 patients using opioids and by Perry and Heidrich,[52] who found no addiction among 10 000 burn patients treated with opioids. Both of these studies, although shedding some light on the risk of addiction for acute pain, do not help establish the risk of iatrogenic addiction when opioids are used daily for a prolonged time in treating chronic pain. There are a number of studies, however, that demonstrate that in the treatment of chronic non–cancer-related pain with opioids, there is a high incidence of prescription drug abuse. Prescription drug abuse in a substantial minority of chronic-pain patients has been demonstrated in studies by Fishbain et al. (3%–18% of patients),[53] Hoffman et al. (23%),[54] Kouyanou et al. (12%),[55] Chabal et al. (34%),[56] Katz et al. (43%),[57] Reid et al. (24%–31%),[58] and Michna et al. (45%).[59] A recent literature review showed that the prevalence of addiction in patients with long-term opioid treatment for chronic non–cancer-related pain varied from 0% to 50%, depending on the criteria used and the subpopulation studied.[60]

Misrepresenting the risk of addiction proved costly for Purdue. On May 10, 2007, Purdue Frederick Company Inc, an affiliate of Purdue Pharma, along with 3 company executives, pled guilty to criminal charges of misbranding OxyContin by claiming that it was less addictive and less subject to abuse and diversion than other opioids, and will pay $634 million in fines.[61]

Although research demonstrated that OxyContin was comparable in efficacy and safety to other available opioids,[11,63] marketing catapulted OxyContin to blockbuster drug status. Sales escalated from $44 million (316 000 prescriptions dispensed) in 1996 to a 2001 and 2002 combined sales of nearly $3 billion (over 14 million prescriptions).[19]

The remarkable commercial success of OxyContin, however, was stained by increasing rates of abuse and addiction. Drug abusers learned how to simply crush the controlled-release tablet and swallow, inhale, or inject the high-potency opioid for an intense morphinelike high.[64] There had been some precedence for the diversion and abuse of controlled-release opioid preparations. Purdue's own MS Contin had been abused in the late 1980s in a fashion similar to how OxyContin was later to be; by 1990, MS Contin had become the most abused prescription opioid in one major metropolitan area.[65] Purdue's own testing in 1995 had demonstrated that 68% of the oxycodone could be extracted from an OxyContin tablet when crushed.[66]

Opioid prescribing has had significant geographical variations. In some areas, such as Maine, West Virginia, eastern Kentucky, southwestern Virginia, and Alabama, from 1998 through 2000, hydrocodone and (non-OxyContin) oxycodone were being prescribed 2.5 to 5.0 times more than the national average. By 2000, these same areas had become high OxyContin-prescribing areas—up to 5 to 6 times higher than the national average in some counties (Table 1).[67] These areas, in which OxyContin was highly available, were the first in the nation to witness increasing OxyContin abuse and diversion, which began surfacing in 1999 and 2000.[23]

From 1995 to 2001, the number of patients treated for opioid abuse in Maine increased 460%, and from 1997 to 1999 the state had a 400% increase in the number of chronic hepatitis C cases reported.[68] In eastern Kentucky from 1995 to 2001, there was a 500% increase in the number of patients entering methadone maintenance treatment programs, about 75% of whom were OxyContin dependent (Mac Bell, administrator, Narcotics Treatment Programs, Kentucky Division of Substance Abuse, written communication, March 2002). In West Virginia, the first methadone maintenance treatment program opened in August 2000, largely in response to the increasing number of people with OxyContin dependence. By October 2003, West Virginia had 7 methadone maintenance treatment clinics with 3040 patients in treatment (M. Moore, Office of Behavioral Health Services, Office of Alcoholism and Drug Abuse, West Virginia, written communication, March 16, 2004). In southwestern Virginia, the first methadone maintenance treatment program opened in March 2000, and within 3 years it had 1400 admissions (E. Jennings, Life Center of Galax, Galax, Virginia, written communication, March 12, 2004).

With increasing diversion and abuse, opioid-related overdoses escalated. In southwest Virginia, the number of deaths related to opioid prescriptions increased 830%, from 23 in 1997 to 215 in 2003 (William Massello III, MD, assistant chief medical examiner, Office of Chief Medical Examiner, Western District, Virginia Department of Health, written communication, January 12, 2007). The high availability of OxyContin in these 5 regions seemed to be a simple correlate of its abuse, diversion, and addiction.

With the growing availability of OxyContin prescriptions, the once-regional problem began to spread nationally. By 2002, OxyContin accounted for 68% of oxycodone sales.[69] Lifetime nonmedical use of OxyContin increased from 1.9 million to 3.1 million people between 2002 and 2004, and in 2004 there were 615 000 new nonmedical users of OxyContin.[70] By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States.[2]

The increasing OxyContin abuse problem was an integral part of the escalating national prescription opioid abuse problem. Liberalization of the use of opioids, particularly for the treatment of chronic non–cancer-related pain, increased the availability of all opioids as well as their abuse. Nationwide, from 1997 to 2002, there was a 226%, 73%, and 402% increase in fentanyl, morphine, and oxycodone prescribing, respectively (in grams per 100 000 population). During that same period, the Drug Abuse Warning Network reported that hospital emergency department mentions for fentanyl, morphine, and oxycodone increased 641%, 113%, and 346%, respectively.[71] Among new initiates to illicit drug use in 2005, a total of 2.1 million reported prescription opioids as the first drug they had tried, more than for marijuana and almost equal to the number of new cigarette smokers (2.3 million).[72] Most abusers of prescription opioids get their diverted drugs directly from a doctor's prescription or from the prescriptions of friends and family.[73]

In terms of illicit drug abuse, prescription opioids are now ahead of cocaine and heroin and second only to marijuana.[72] Mortality rates from drug overdose have climbed dramatically; by 2002, unintentional overdose deaths from prescription opioids surpassed those from heroin and cocaine nationwide.[74] Nationally, as well as regionally, the high availability of OxyContin and all prescription opioids was correlated with high rates of abuse and diversion.

THE FOOD AND DRUG ADMINISTRATION

Under the Food, Drug, and Cosmetics Act and implementing regulations, the FDA regulates the advertising and promotion of prescription drugs and is responsible for ensuring that prescription drug advertising and promotion are truthful, balanced, and accurately communicated. There is no distinction in the act between controlled and noncontrolled drugs regarding the oversight of promotional activities. Although regulations require that all promotional materials for prescription drugs be submitted to the FDA for review when the materials are initially disseminated or used, it is generally not required that these materials be approved by the FDA prior to their use. The FDA has a limited number of staff for overseeing the enormous amount of promotional materials. In 2002, for example, 39 FDA staff members were responsible for reviewing roughly 34 000 pieces of promotional materials.[19] This limited staffing significantly diminishes the FDA's ability to ensure that the promotion is truthful, balanced, and accurately communicated.

In 1998, Purdue distributed 15 000 copies of an OxyContin video to physicians without submitting it to the FDA for review, an oversight later acknowledged by Purdue. In 2001, Purdue submitted to the FDA a second version of the video, which the FDA did not review until October 2002—after the General Accounting Office inquired about its content. After its review, the FDA concluded that the video minimized the risks from OxyContin and made unsubstantiated claims regarding its benefits to patients.[19]

When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain. In July 2001, to reflect the available scientific evidence, the label was modified to state that data were not available for establishing the true incidence of addiction in chronic-pain patients. The 2001 labeling also deleted the original statement that the delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.[19] A more thorough review of the available scientific evidence prior to the original labeling might have prevented some of the need for the 2001 label revision.

CONCLUSIONS

OxyContin appears to be as efficacious and safe as other available opioids and as oxycodone taken 4 times daily.[11,63] Its commercial success, fueled by an unprecedented promotion and marketing campaign, was stained by escalating OxyContin abuse and diversion that spread throughout the country.[2,75] The regions of the country that had the earliest and highest availability of prescribed OxyContin had the greatest initial abuse and diversion.[23,67] Nationally, the increasing availability of OxyContin was associated with higher rates of abuse, and it became the most prevalent abused prescription opioid by 2004.[2]

Compared with noncontrolled drugs, controlled drugs, with their potential for abuse and diversion, pose different public health risks when overpromoted and highly prescribed. Several marketing practices appear to be especially questionable.

The extraordinary amount of money spent in promoting a sustained-release opioid was unprecedented. During OxyContin's first 6 years on the market, Purdue spent approximately 6 to 12 times more on promoting it than the company had spent on promoting MS Contin, or than Janssen Pharmaceutical Products LP had spent on Duragesic, one of OxyContin's competitors.[19] Although OxyContin has not been shown to be superior to other available potent opioid preparations,[11,63] by 2001 it had become the most frequently prescribed brand-name opioid in the United States for treating moderate to severe pain.[19] Carefully crafted limits on the marketing and promotion of controlled drugs would help to realign their actual use with the principles of evidence-based medicine.

Physicians' interactions with pharmaceutical sales representatives have been found to influence the prescribing practices of residents and physicians in terms of decreased prescribing of generic drugs, prescribing cost, nonrational prescribing, and rapid prescribing of new drugs.[76] Carefully crafted limits on the promotion of controlled drugs by the pharmaceutical sales force and enhanced FDA oversight of the training and performance of sales representatives would also reduce over- and misprescribing.

Although there are no available data for evaluating the promotional effect of free starter coupons for controlled drugs, it seems likely that the over- and misprescribing of a controlled drug are encouraged by such promotional programs and the public health would be well served by eliminating them.

The use of prescriber profiling data to influence prescribing and improve sales is imbedded in pharmaceutical detailing. Very little data are publicly available for understanding to what extent this marketing practice boosts sales. One market research report indicated that profiling improved profit margins by as much as 3 percentage points and the initial uptake of new drugs by 30%.[77] The use of prescriber profiling data to target high-opioid prescribers—coupled with very lucrative incentives for sales representatives—would seem to fuel increased prescribing by some physicians—perhaps the most liberal prescribers of opioids and, in some cases, the least discriminate. Regulations eliminating this marketing tool might decrease some potential overprescribing of controlled drugs.

The public health would be better protected if the FDA reviewed all advertising and promotional materials as well as associated educational materials—for their truthfulness, accuracy, balance, and scientific validity—*before* dissemination. Such a change would require a considerable increase in FDA support, staffing, and funding from what is currently available. Public monies spent on the front end of the problem could prevent another such tragedy.

The pharmaceutical industry's role and influence in medical education is problematic. From 1996 through July 2002, Purdue funded more than 20 000 pain-related educational programs through direct sponsorship or financial grants,[19] providing a venue that had enormous influence on physicians' prescribing throughout the country. Particularly with controlled drugs, the potential for blurring marketing and education carries a much higher public health risk than with uncontrolled drugs. At least in the area of controlled drugs, with their high potential for abuse and diversion, public health would best be served by severing the pharmaceutical industry's direct role and influence in medical education.

Marketing and promotion by the pharmaceutical industry have considerably amplified the prescription sales and availability of opioids. A number of factors have contributed to the marked growth of opioid abuse in the United States, but one factor is certainly the much increased availability of prescription opioids.[78] The public interest and public health would be better served by a redefinition of acceptable and allowable marketing practices for opioids and other controlled drugs. ■

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This article was accepted May 9, 2008.

Acknowledgments

I thank Michael McNeer, MD, for his thoughtful review of the essay and helpful suggestions.

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